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Cyclobutanone Mimics of Penicillins: Effects of Substitution on Conformation and Hemiketal Stability

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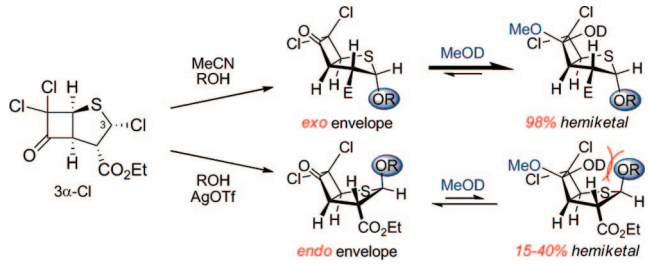

The tendency for carbocyclic analogues of penicillins to undergo hydrate and hemiketal formation is central to their ability to function as β-lactamase inhibitors. 2-Thiabicyclo[3.2.0]heptan-6-one-4-carboxylates with alkoxy functionality at C3 have been prepared through two complementary diastereoselective substitution reactions following a highly stereoselective chlorination with sulfuryl chloride. We have found that carbocyclic analogues with 3β substituents favor an *endo* envelope conformation in solution, the solid state, and the gas phase, whereas those with 3α substituents adopt an *exo* envelope. Evidence from X-ray crystal structures and ab initio calculations suggests that an anomeric effect contributes to the large conformational preference of the tetrahydrothiophene ring that favors the C3 substituent in an axial orientation. In addition, the envelope conformation of the bicycle, which is determined by the stereochemistry of the C3 substituent, has a dramatic effect on the ability of the cyclobutanone to undergo hemiketal formation in methanol-d_4.

Introduction

β-Lactam antibiotics have been the most widely used antibacterial agents for several decades, but the continued effectiveness of these agents is threatened by increasing bacterial resistance.[1] This has become a serious problem worldwide and is especially worrisome in hospital-acquired infections. The most significant mode of resistance is the expression of β-lactamases, enzymes that have the ability to efficiently inactivate β-lactams through hydrolysis.[2]

These enzymes are divided into four classes on the basis of sequence homology.[3] The class A, C, and D β-lactamases rely on an active-site serine residue as a nucleophile and achieve turnover through the formation of an acyl enzyme intermediate and subsequent hydrolytic deacylation (Figure 1). The zinc-dependent class B enzymes, which have been termed metallo-β-lactamases (MBLs), do not form a covalently bound acyl

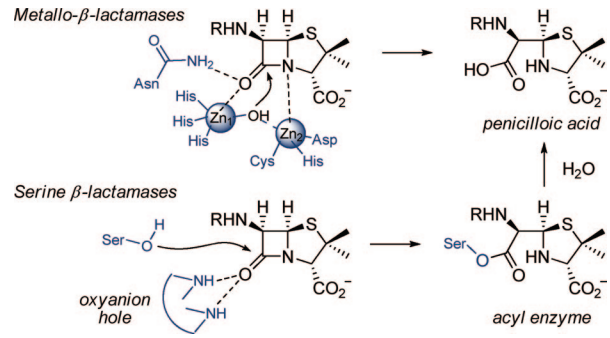

FIGURE 1. Hydrolysis of a penicillin by β-lactamases.

† Deceased November 2006.

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(3) Ambler, R. P. *Philos. Trans. R. Soc. London, Ser. B* **1980**, *289*, 155–165.

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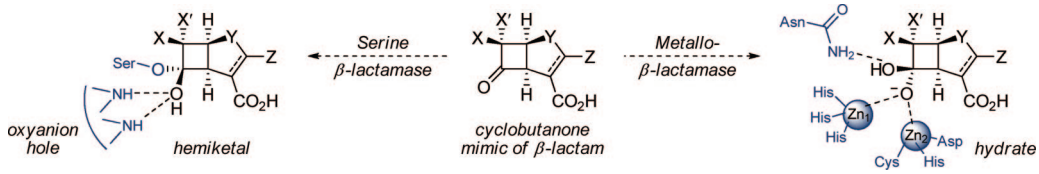
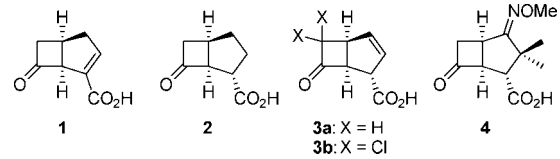


FIGURE 2. Cyclobutanones as potential broad-spectrum inhibitors of β-lactamases.

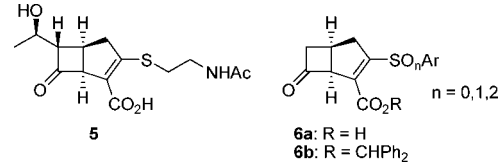
enzyme intermediate since the active-site nucleophile is a zinc-bound water (or hydroxide).[4]

One strategy for overcoming β-lactamase-mediated resistance has involved the use of a β-lactamase inhibitor such as clavulanate, sulbactam, or tazobactam, in combination with the β-lactam antibiotic.[5,6] Another successful approach has involved the development of β-lactams, such as the extended-spectrum penicillins and cephalosporins and the carbapenems, which are less susceptible to β-lactamase hydrolysis and maintain broad antibiotic activities. While therapies employing these β-lactams have been successful against bacteria producing class A and class C serine β-lactamases, they are less effective against those producing the class D "OXA" enzymes[7] and not effective against the class B metallo-β-lactamase producers.[8] More importantly, the MBLs,[9] some OXA-type β-lactamases,[10] and a clinically important group of class A enzymes called KPCs[11] possess the ability to hydrolyze carbapenems,[12] the β-lactams that have been used as the last line of defense against multidrug resistant organisms.[13] Currently, there are no inhibitors of metallo-β-lactamases available for clinical use.[14]

Cyclobutanones. In the 1980s, several research groups proposed independently that analogues of β-lactams in which the β-lactam ring is replaced by a cyclobutanone system might inhibit serine β-lactamases and DD-transpeptidases by virtue of their ability to form an enzyme-bound hemiketal[15] with an active-site serine residue (Figure 2).[16] As early as 1981, Gordon et al. reported the synthesis of cyclobutanones **1**−**3** for this purpose but found no significant inhibition of either R-TEM β-lactamase or R61 transpeptidase.[17] Meth-Cohn et al. synthesized cyclobutanone **4** but did not disclose any biochemical or biological data.[18]



A subsequent publication by Cocuzza and Boswell described the synthesis of several cyclobutanone derivatives, including **5** and **6**, but none of the free acids demonstrated anti-β-lactamase activity.[19,20]



Studies by Lowe and Swain, however, indicated that 2-oxabicyclo[3.2.0]heptanones **7** and **8** showed slow, time-dependent inhibition of the class A β-lactamases R-TEM-2 and BcI, and **8** demonstrated activity against R61 transpeptidase.[21] Our laboratory described the preparation of dichlorocyclobutanone **9**,[22] and Kelly et al. reported that **9** was a weak competitive inhibitor (K_i = 1 mM) of R61 transpeptidase.[23−25] Although the preliminary biochemical data served as a proof of principle for the concept that cyclobutanones might be reasonable mimics of the penicillins, other more impressive advances in the inhibition of class A β-lactamases, which led to the clinically very useful clavulanic acid and sulbactam, discouraged further explorations of the cyclobutanones in this context.

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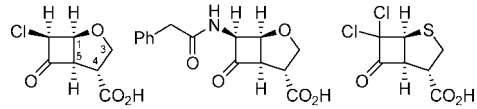
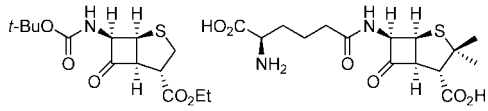


7 8 9

The emergence of serine and metallo-β-lactamases with a broad spectrum of activity encompassing all known classes of β-lactam antibiotics requires renewed efforts to establish strategies with potential for overcoming this growing threat through development of broad spectrum β-lactamase inhibitors that are effective against both the serine and the metallo-β-lactamases.[26] Cyclobutanones of the type indicated above have the potential for formation of not only an enzyme-bound hemiketal in the active site of serine β-lactamases but also an enzyme-bound hydrate in the active site of a metallo-β-lactamase and hence represent a core structure that might form the basis for the design of broad spectrum β-lactamase inhibitors. Previous studies have yielded only a superficial understanding of the properties of such systems, which provides little guidance for renewed efforts to exploit this potential. We report herein the results of a systematic experimental and theoretical exploration of the influence of the structure of such bicyclic cyclobutanones on their conformations and on their tendencies to form hemiketals and hydrates, which should assist the rational design of more effective β-lactamase inhibitors based on this general strategy.

Results and Discussion

The synthetic route used for the preparation of 2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylates involved a [2 + 2] cycloaddition with dichloroketene as previously reported by our group[22] and later used by the Baldwin group for the synthesis of **10** and **11** (Scheme 1).[27]



10 11

Phosphonate **13**, generated in high yield by the Michaelis−Arbuzov reaction of **12** with triethylphosphite, was treated with paraformaldehyde and piperidine before dehydration with *p*-toluenesulfonic acid in toluene under Dean−Stark conditions. The vinyl phosphonate **14** was combined with 2,5-dihydroxy-1,4-dithiane and triethylamine, in a procedure developed by McIntosh and Sieler,[28] to achieve a one-pot conjugate addition and intramolecular Horner−Wadsworth−Emmons cyclization. Saponification of the ester **15**, followed by treatment of the acid **16** with triethylamine and ethyl chloroformate provided ester **17** through a deconjugation procedure which likely proceeds through deprotonation and decarboxylation of a mixed anhydride intermediate, followed by addition of ethanol to the unsaturated ketene generated.[29]

The deconjugated dihydrothiophene **17** was then subjected to a fully regioselective [2 + 2] cycloaddition with dichloroketene,[30−32] which was generated in situ from dichloroacetyl chloride and triethylamine. As dichlorocyclobutanones are known to be sensitive to base-induced ring cleavage,[17,33] conversion of **18** to the carboxylic acid **9** was accomplished with acid catalysis. The ester **18** and the acid **9** were readily dechlorinated with excess zinc dust in acetic acid to give cyclobutanones **19** and **20**, respectively, in good yield.

The cyclobutanones **9** and **18**−**20** were all found to prefer an *endo* envelope in solution as indicated by the lack of coupling between H4 and H5 in the ^{1}H NMR spectra. Examination of molecular models indicated that the dihedral angle between H4 and H5 would be close to 90° in this conformation only. X-ray crystallographic analysis and ab initio molecular orbital calculations (RHF, vide infra) later confirmed this conformational preference for acids **9** and **20** in the solid state (Figure 3) and gas phase, respectively. NMR analysis of cyclobutanones **7** and **8** led Lowe and Swain to recognize that an *endo* envelope is also preferred by the 2-oxa ring system.[21]

Hydrate and Hemiketal Formation. Several biochemical studies since the 1970s have shown that peptide aldehydes[34] and α-fluorinated ketones[35,36] are potent inhibitors of serine-, cysteine-, and metalloproteases[37] and, more recently, metallo-β-lactamases.[38] Enzyme-bound tetrahedral adducts of these so-

(27) The Baldwin group synthesized carbocyclic analogues of penicillin N for studies with deacetoxycephalosporin C synthase (DAOCS) using this route (Scheme 1) in combination with the intramolecular nitrene C-H insertion method developed by Lowe and Swain.[21] (a) Martyres, D. H.; Baldwin, J. E.; Adlington, R. M.; Lee, V.; Probert, M. R.; Watkin, D. J *Tetrahedron* **2001**, *57*, 4999–5007. (b) Ferguson, A. C.; Adlington, R. M.; Martyres, D. H.; Rutledge, P. J.; Cowley, A.; Baldwin, J. E. *Tetrahedron* **2003**, *59*, 8233–8243.

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(29) Deconjugation under these mild conditions is a method that has shown some generality. Straight-chain as well as carbocyclic α,β-unsaturated acids can also undergo deconjugation, but the process is slower and can generate significant amounts of the conjugated ester. Ethyl chloroformate seems to be more effective than methyl and benzyl chloroformate.

(30) It is not yet clear whether the cyclobutanone-forming reaction proceeds via a concerted process or via a stepwise pathway. In any event, the regioselectivity of the cycloaddition is compatible with that expected for a dipolar transition-state in which partial positive charge is developed at C5 of the dihydrothiophene and stabilized by interaction with the sulfur atom.

(31) In addition to the [2 + 2] cycloaddition involving the ketene C═C bond, which would lead directly to the cyclobutanone product, recent studies have identified the possibility of a competing [2 + 2] cycloaddition, which involves the ketene C═O bond. The initially formed oxetane product then rearranges through a zwitterionic intermediate to provide the cyclobutanone product. (a) Machiguchi, T.; Okamoto, J.; Takachi, J.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2003**, *125*, 14446–14448. (b) Machiguchi, T.; Okamoto, J.; Morita, Y.; Hasegawa, T.; Yamabe, S.; Minato, T. *J. Am. Chem. Soc.* **2006**, *128*, 44–45.

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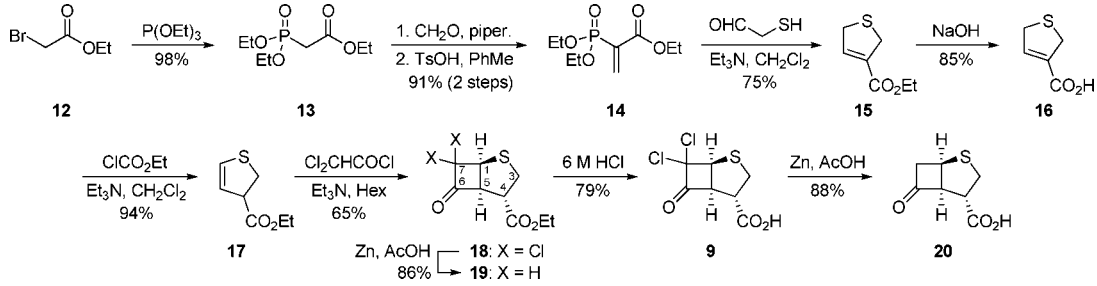
SCHEME 1. Synthetic Route to 2-Thiabicyclo[3.2.0]heptan-6-one-4-carboxylate Derivatives[a]



[a] Mercaptoacetaldehyde is commercially available as its dimer, 2,5-dihydroxy-1,4-dithiane.

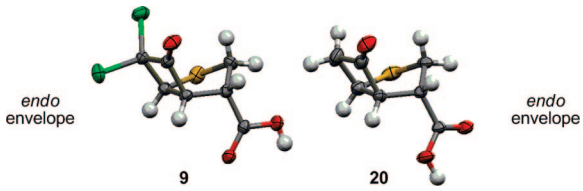


FIGURE 3. X-ray crystal structures of **9** and **20**. Color scheme: white, gray, red, yellow, and green represent H, C, O, S, and Cl, respectively.

called transition-state analogues[39] have been observed spectroscopically and crystallographically.[40]

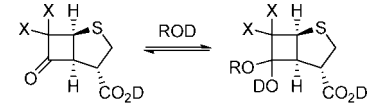
The superior inhibition of serine proteases by di- and trifluoromethyl ketones relative to that of the mono- and nonfluorinated ketones[35] is a clear indication of the importance of the stability of the enzyme-bound hemiketal (or hydrate).[41] Interestingly, the K_i values reported by Gelb et al. for trifluoromethyl ketones with acetylcholinesterase (16 nM) and carboxypeptidase A (0.2 nM) demonstrate that these electrophilic carbonyl compounds can be potent and effective inhibitors of both serine proteases and zinc-dependent enzymes despite the fact that they are nearly entirely hydrated in aqueous solution.[35a]

Similarly, the effectiveness of cyclobutanones as β-lactamase inhibitors is expected to be highly dependent upon the stability of the enzyme-bound tetrahedral intermediate mimic, and it occurred to us that the extent of hydration and hemiketal formation in water and alcohol could serve as an estimate of the relative stability of the tetrahedral adducts and might be used in the rational design of inhibitors.

The tendency of the 2-thiabicyclo[3.2.0]heptan-6-one system to undergo hydration and hemiketal formation was evaluated by NMR experiments involving the free acids **9** and **20** in D_2O[42] or CD_3OD (Table 1). The dichlorocyclobutanone **9** (δ_{C6} 198) quickly formed the hydrate (δ_{C6} 99) in D_2O and reached a ketone:hydrate equilibrium ratio of 26:74 within 5 min, but the dechlorinated acid **20** did not undergo any measurable hydration. Similarly, the corresponding experiments in methanol-d_4 showed a greater extent of hemiketal formation with **9** than with **20** and that each ketone formed the hemiketal to a greater extent than the hydrate.[43]

Derivatives. Access to C3-substituted variants of the 2-thiabicyclo[3.2.0]heptan-6-one system was achieved through

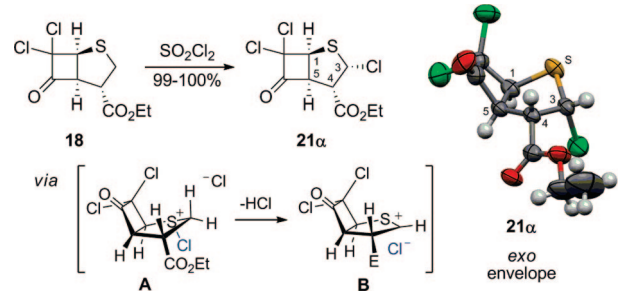
TABLE 1. Hydrate and Hemiketal Formation with 9 and 20[a]



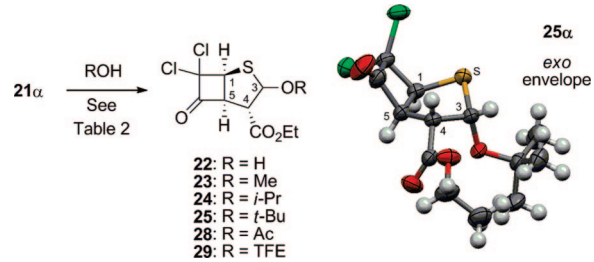
ketone	% hydrate	% hemiketal
9	74	88
20	0	24

[a] Percentage of hydrate formation was determined by ^{1}H NMR in D_2O/acetone-d_6,[42] and hemiketal formation was determined in methanol-d_4.

SCHEME 2. Chlorination of 18 and X-ray Structure of 21α



SCHEME 3. Solvolysis of 21α and X-ray Structure of 25α



the regioselective chlorination of **18** with sulfuryl chloride,[44] which furnished **21α** in excellent yield and with high stereoselectivity (Scheme 2). The stereoselectivity of the process may be a consequence of the initial chlorination of **18** occurring on the *exo* face to generate the *S*-chlorosulfonium ion **A**. Elimination of HCl might then lead to the sulfur-stabilized carbocation **B** with the chloride leaving group poised for subsequent attack from the *exo* face of the ring system, which would provide the 3α-chloride **21α**.

It was clear from the ^{1}H NMR spectrum of **21α** that the conformation was different from that of **9** and **20** since the

(41) Fluorination not only stabilizes the hemiketal (relative to the ketone) but also reduces the pK_a of the hemiketal (pK_a ~4.9 within chymotrypsin) and results in a more effective transition-state analogue.[40f]

(42) A small amount of acetone-d_6 was used to facilitate solubilization. The ratio D_2O:acetone-d_6 was approximately 3:1.

(43) Several other ketones and aldehydes, including cyclobutanone, have also been shown to form hemiketals more extensively than hydrates: Wiberg, K. B.; Morgan, K. M.; Maltz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11067–11077.

(44) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572–577.

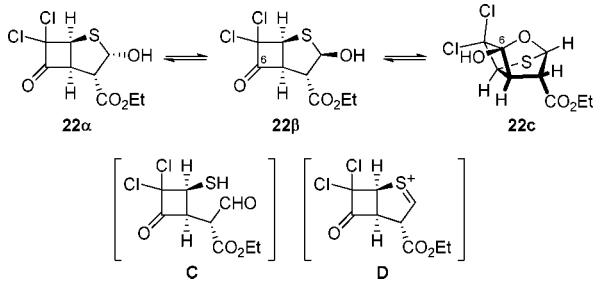


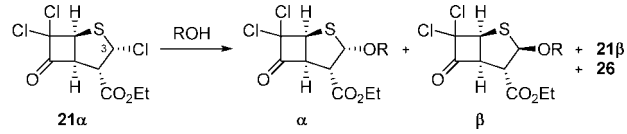
FIGURE 4. An equilibrium involving **22α**, **22*β***, and **22c**.

coupling constant between H4 and H5 was found to be 6 Hz ($J_{4,5} \approx 0$ Hz for **9** and **20**). The stereochemistry and *exo* envelope conformation for **21α** were confirmed by a single-crystal X-ray diffraction study (see Scheme 2).

Substitutions. It was found that the solvolysis of **21α** could be accomplished in either water or alcohol with the use of acetonitrile as a polar and miscible cosolvent to provide the 3-alkoxy (*S*,*O*-acetal) substitution products (Scheme 3). Hydrolysis of **21α** generated the thiolactols **22α** and **22*β*** in a ratio of 1:14, respectively, which could not be separated by flash chromatography. Interestingly, ^{1}H and ^{13}C NMR spectra of the chromatographed thiolactol mixture showed a third material (~6%) that was identified as a tricyclic intramolecular hemiketal **22c** (δ_{C6} 105.9) (Figure 4).[45,46] Since the **22α**:**22*β***:**22c** ratio was consistently close to 6:88:6 in several different preparations, it is thought that the mixture may be part of an equilibrium that allows the interconversion of **22α** and **22*β***. In order to gain insight into the mechanism of interconversion, an NMR experiment was conducted in which the thiolactol mixture **22** was subjected to acidic methanol-d_4/acetonitrile-d_3 (1:1).[47] The lack of any cross-over reactions under the reaction conditions (to generate **23α** or **23*β***) suggests that equilibration via ring-opened aldehyde **C** is more likely than equilibration through a sulfur-stabilized carbocation **D**.

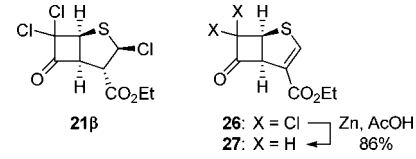
Similar to the hydrolysis, the solvolysis reaction of **21α** in methanol/acetonitrile was complete within 48 h and cleanly generated the substitution products **23α** and **23*β*** (Table 2). However, the reactions with sterically demanding alcohols, 2-propanol and *tert*-butyl alcohol, showed incomplete conversion and generated considerably more of the epimerization and elimination byproduct, **21*β*** and **26**.[48] The unsaturated ester **26** could be prepared separately through dehydration of the thiolactol **22*β*** with TsOH in refluxing toluene under Dean−Stark conditions and was dechlorinated with zinc in acetic acid to give **27**.[49]

TABLE 2. Substitutions at C3 with Alcohols and AcOH[a]



solvent(s)	time (h)	product	OR	α[b]	*β*	21*β*	26
MeCN/H_2O 1:1	48	**22**	OH[c]	6	88	0	0
MeCN/MeOH 1:1	48	**23**	OMe	75	24	0	1
MeCN/*i*-PrOH 1:1	40	**24**	O*i*-Pr[d]	46	20	16	18
MeCN/*t*-BuOH 1:1	48	**25**	O*t*-Bu[e]	34	7	44	15
AcOH	48	**28**	OAc	3	52	43	2
AcOH, 80 °C	1	**28**	OAc	4	79	6	11
CF_3CH_2OH	48	**29**	OTFE	5	76	0	19

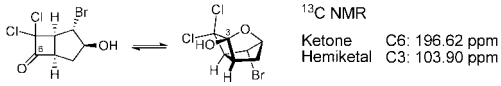
[a] Reactions were performed at room temperature unless otherwise stated. [b] Product distributions were determined by ^{1}H NMR of the crude product. [c] Remaining 6% is attributed to **22c**. [d] 85% conversion. [e] 42% conversion.



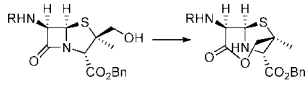
In contrast to the hydrolysis, the substitutions in MeOH, *i*-PrOH, and *t*-BuOH selectively produced the α-OR retention products. The results of additional control experiments in acidic methanol-d_4/acetonitrile-d_3 discount the possibility that the α-OR products are the result of the conjugate addition of ROH to **26**,[50] demonstrate that equilibration of the substitution products α-OR and *β*-OR does not occur,[51] and imply that the α/*β* ratios are the consequences of kinetic and not thermodynamic control.

The high α-selectivity in the substitution with methanol led us to speculate that a cyclobutanone hemiketal could be generated that would block the *endo* face of C3 from subsequent inversion (structures **E** and **F**, Figure 5). In this way, attack from the *exo* (α) face of **F** would lead to the major isomer **23α** whereas the minor isomer **23*β*** would be a result of attack from the *endo* (*β*) face of **D**. In addition, we considered the possibility that the hemiketal could provide higher α selectivity through a double inversion resulting from neighboring group participation (structures **G** and **H**). Work reported by Grudzinski and

(45) An oxatricyclo[3.2.1.0^{3,6}]octane has been observed previously: (a) Grudzinski, Z.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1767–1773. X-ray study: (b) Glen, R. C.; Murray-Rust, P.; Riddell, F. G.; Newton, R. F.; Kay, P. B. *J. Chem. Soc., Chem. Commun.* **1982**, 25–26. (c) Isaacs, N. S.; Rzepa, H. S.; Sheppard, R. N.; Lobo, A. M.; Prabhakar, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1477–1482.



(46) A related intramolecular attack by an alcohol has also been observed in *β*-lactam systems: Baldwin, J. E.; Cobb, J. E.; Sheppard, L. N *Tetrahedron* **1987**, *43*, 1003–1012.



(47) The thiolactol mixture **22α**:**22*β***:**22c** was dissolved in acetonitrile-d_3 and methanol-d_4 (1:1, 1 mL total) and combined with acetyl chloride (1.5 equiv, 0.05 M) to generate HCl in situ. Neither of the cross-over products **23α** or **23*β*** were detected after 48 h at room temperature. Removal of the solvents provided **22** in the same 6:88:6 ratio.

(48) The 3*β*-Cl epimer **21*β*** could not be made or isolated in useful quantities for further studies since it was found to be unstable to chromatography. However, **21*β*** was found to prefer an *endo* envelope conformation in solution, as indicated by the multiplicity of H3 and H4 in the ^{1}H NMR spectrum. As with **28*β***, H3 and H4 in **21*β*** appear as singlets and $J_{3\alpha,4} = 0$ Hz.

(49) Elimination of HCl from **21α** could not be effected under basic conditions with pyridine, Et_3N, or DBU, in CH_2Cl_2, THF, or MeCN. Heating **21α** in MeCN achieved partial elimination, but the epimer **21*β*** was observed as a major byproduct that showed even slower elimination (by NMR). The use of $AgCO_3$ resulted in a complex mixture with only a low yield of the elimination product **26**.

(50) Ester **26** was dissolved in CD_3OD/CD_3CN (1:1) with AcCl (1.3 equiv, 0.1 M). While a large amount of hemiketal was observed (93%), none of the addition products **23α** or **23*β*** were detected after 6 d.

(51) Cyclobutanone **23α** was dissolved in isopropanol-d_8/acetonitrile-d_3 (1:1) and treated with AcCl (to give 0.1 M HCl). After 4 d at room temperature none of the possible cross-over products **24α** or **24*β*** were detected and **23α** was recovered. Separately, **23*β*** was subjected to the same conditions and no reaction was observed after 4 d at room temperature.

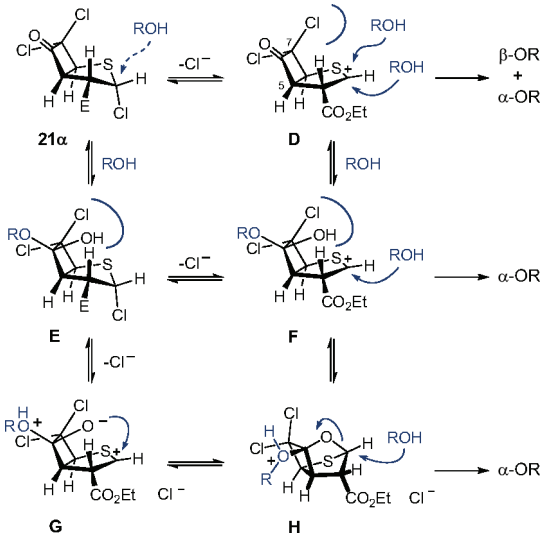


FIGURE 5. Possible intermediates in substitutions involving **21α** with ROH (E = CO_2Et).

Roberts[52] involving the bromination of similar bicyclic substrates indicates that this pathway is plausible.[53]

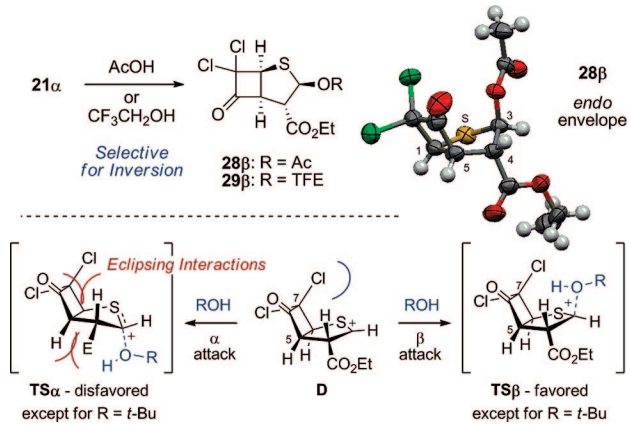
While the hypothesis involving intermediates **E**−**H** is reasonable for methanol,[54a] hemiketal formation with a bulkier alcohol such as *tert*-butanol is less significant.[54b] It is likely that the retention product **25α** is the result of attack by *tert*-butanol on intermediate **D**, in which the *exo* face is more accessible than *endo* face as a consequence of steric shielding by the 7*β*-chlorine.[55] The rationale that steric hindrance drives the 5:1 α:*β* selectivity would be consistent with the lower conversion observed in the reaction with *tert*-butanol.

The 2:1 α:*β* selectivity shown by 2-propanol could be rationalized by a combination of its capability to slowly form the hemiketal,[54c] which would lead to **24α** from **F** or **H**, and its ability to attack from the *endo* (*β*) face of **C** or **D**, which would yield **24*β***.

The high selectivity in favor of inversion demonstrated by acetic acid (**28α**:**28*β*** ≈ 1:17) and trifluoroethanol (**29α**:**29*β*** ≈ 1:15) was unexpected as it clearly contrasts with that of the aforementioned alcohols. This selectivity suggests that attack from the *endo* face must be favored electronically since the enhanced acidity and weaker nucleophilicity of AcOH and TFEOH[54d] increase the S_N1 character of the substitution relative to reactions with ordinary alcohols (Scheme 4).

Attack on the carbocation from the α (*exo*) face may be disfavored as a result of two destabilizing eclipsing interactions in **TSα** that are not present in **TS*β***. The high α selectivity demonstrated by *t*-BuOH, however, indicates that the 7*β*-Cl imposes such a large destabilizing steric interaction in **TS*β*** that **TSα** is preferred.

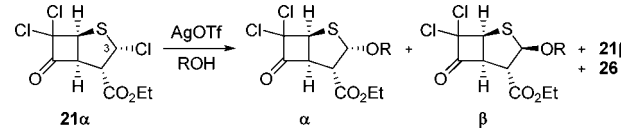
SCHEME 4. Solvolysis of 21α with AcOH and TFEOH, X-ray Structure of 28*β*, and Rationale for Selectivity



Substitutions Promoted by Silver Triflate. While the solvolysis reactions using ROH/MeCN were useful for the synthesis of **22*β*** and **23α**−**25α** and interesting from a mechanistic point of view, they generally required relatively long reaction times and difficult chromatographic separations and generated large proportions of the epimerization and elimination byproduct **21*β*** and **26**. Efforts were then made to develop a complementary method that would be more selective for inversion and improve upon the reaction times and the amount of byproduct formed. The use of silver triflate was explored (Table 3), as it has been used as a promoter in substitutions at the anomeric position of chlorocarbohydrates.

Since the α/*β* selectivity of the hydrolysis was not a concern (based on the proposed interconversion of the products **22α** and **22*β***), acetonitrile was chosen as a water-miscible solvent.[56] However, the use of MeCN with **21α** was otherwise considered problematic due to the spontaneous epimerization to **21*β*** observed previously[49] and CH_2Cl_2 was used for reactions with alcohols. Typically, **21α** was slowly added as a solution in CH_2Cl_2 to a suspension of AgOTf, ROH, and molecular sieves in CH_2Cl_2 at 0 °C.

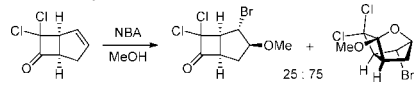
TABLE 3. Substitutions at C3 Promoted by Silver Triflate[a]



ROH	equiv ROH	time (h)	product	OR	α[b]	*β*	21*β*	26
H_2O [c]	excess	4	**22**	OH[d]	6	85	0	3
MeOH	5	6	**23**	OMe	22	72	2	4
MeOH	10	6	**23**	OMe	26	61	0	2
i-PrOH	5	12	**24**	O*i*-Pr	16	71	2	11
t-BuOH	10	8	**25**	O*t*-Bu[e]	5	42	30	22

[a] Reaction conditions: AgOTf (1.2 equiv) in CH_2Cl_2 was used with 4 Å MS (3 Å MS for R = Me). Reactions were begun at 0 °C and allowed to warm to room temperature. [b] Product distributions were determined by ^1H NMR of the crude product. [c] Hydrolysis was performed at room temperature in MeCN/H_2O 1:1 without the use of molecular sieves. [d] Remaining 6% is attributed to **22c**. [e] 92% conversion.

(52) The bromination of several bicyclo[3.2.0]hept-2-ene-6-ones in methanol and water was studied by Grudzinski and Roberts.[45a]



(53) The fact that a tricyclic methyl ketal (neutral form of **H**) was not observed may indicate that either this is a minor pathway, or that **H** is very reactive. Note that a full 1 equiv of HCl is generated in this solvolysis reaction while the brominations by Grudzinski and Roberts using *N*-bromoacetamide were nonacidic.

(54) Cyclobutanone **26** was dissolved in deuterated alcohols so that hemiketal formation could be observed by NMR. (a) Methanol-d_4: 96% hemiketal in 2 h; 96% after 4 d. (b) *tert*-Butanol-d_{10}: less than 1% hemiketal after 24 h; 5% after 18 d. (c) Isopropanol-d_8: 7% hemiketal in 5 h; 36% after 8 d. (d) Trifluoroethanol-d_3: less than 1% hemiketal after 4 h; 3% after 8 d.

(55) The five-membered ring is essentially flat in structure **D** (RHF/6-31G(d)). See Table S4 (Supporting Information) for Cartesian coordinates.

(56) The spectra for the **22α**:**22*β***:**22c** mixture isolated from the AgOTf reaction were identical to material obtained from previous preparations.

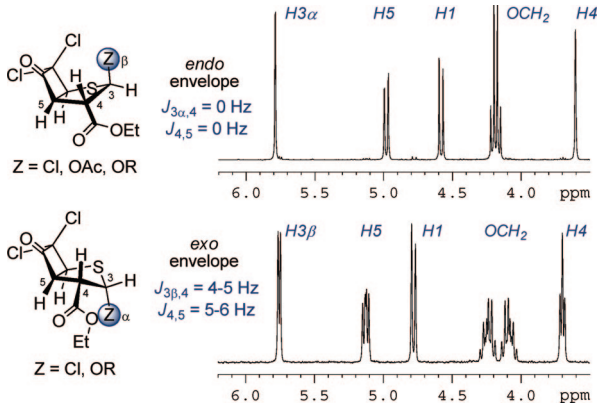


FIGURE 6. Conformations of C3-substituted cyclobutanones. Coupling patterns in the ^{1}H NMR spectra shown (**25*β***and **25α**, Z = O*t*-Bu) are representative of derivatives **21**−**25**, **28**, and **29**.

Indeed, the AgOTf-promoted reactions displayed improved reaction times and an increased selectivity for inversion with ROH. Interestingly, 10 equiv of methanol showed less selectivity for inversion than 10 equiv of *tert*-butanol. Since a decrease to 5 equiv of MeOH improved the β selectivity, it is possible that hemiketal formation remains significant at low concentrations of MeOH and that leakage to **23α** could be through structures **F**−**H** (and to a lesser extent **D**).

The proportion of the elimination byproduct **26** remained a concern in the AgOTf-catalyzed reactions with the hindered nucleophiles *i*-PrOH and *t*-BuOH. This observation inspired an investigation into whether the elimination could be effected exclusively in the absence of a nucleophile. To our satisfaction, the addition of **21α** to AgOTf in refluxing CH_2Cl_2 cleanly furnished **26** in 86% isolated yield.

Conformations of C3-Substituted Cyclobutanone Derivatives. During the development of the solvolysis reactions and silver triflate substitutions it became clear that cyclobutanones with 3α substituents (Z = Cl, *O*-alkyl) conformed to an *exo* envelope, while those with 3β substituents (Z = H, Cl, OAc, *O*-alkyl) showed preference for the *endo* envelope. This was apparent from ^{1}H NMR spectroscopy (Figure 6), as the spectrum of each derivative displayed a pattern similar to that of either **21α** and **25α** or **28*β***, the structures of which have been solved by X-ray crystallographic studies.

We considered the possibility that the conformational preferences could be a result of an anomeric effect involving the sulfur and the electron-withdrawing substituents at C3.[57] Although the conformational properties of sulfur-containing six-membered rings are well-known,[57,58] the anomeric effect has been studied relatively little in five-membered rings since the conformational consequences are much less dramatic and twisted conformations are typically favored in which the substituents are in pseudoaxial or pseudoequatorial orientations. While this is evident in the crystal structures of numerous 4′-thionucleoside derivatives (α-aza substituents),[59] anomeric effects and gauche effects have been argued previously for rationalization of the conformations

(57) Anomeric effect: (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: New York, 1983. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer Verlag: Berlin, 1983. (c) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, 1995. (d) Juaristi, E. *Conformational Behaviour of Six-Membered Rings*; VCH Publishers: New York, 1995.

(58) (a) Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 39–97. (b) Pericas, M. A.; Riera, A.; Guilera, J. *Tetrahedron* **1986**, *42*, 2717–2724.

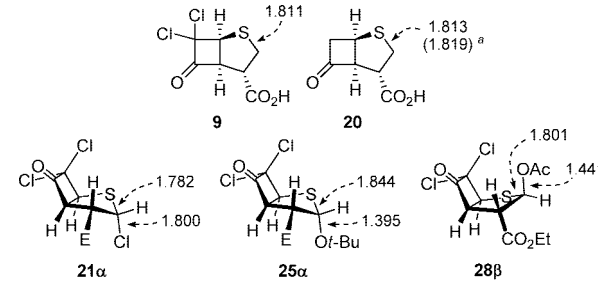


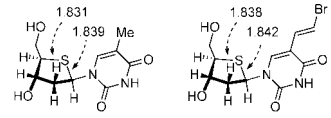
FIGURE 7. Bond lengths (Å) obtained from X-ray crystal structures. The X-ray structure of **20** shows two crystallographically different molecules in the unit cell.

of 4′-thionucleosides.[59,60] In addition, it is possible that anomeric effects are responsible for the axial arrangements that have been recognized by ^{1}H NMR analysis in several known α-halo and α-alkoxy tetrahydrothiophenes.[61]

Since the anomeric effect is often characterized by a shortening of the O−C bond and lengthening of the C−X bond in the O−C−X segment of carbohydrate derivatives, the bond lengths obtained in the X-ray crystal structures of **21α**, **25α**, and **28*β*** were examined closely (Figure 7). Indeed, structural evidence for the anomeric effect was discovered in 2-thiabicyclo[3.2.0]-heptan-6-ones that possess electron-withdrawing substituents at C3.[62]

The 3α-Cl derivative **21α** clearly displays a shortened S−C3 bond (1.782 Å) and a lengthened C3−Cl bond (1.800 Å) in comparison to structurally related tetrahydrothiophenes,[59] dithianes and dioxanes,[63a,c] chlorocarbohydrates,[63d] and the unsubstituted cyclobutanones **9** and **20**. Similarly, the solid-state structure of **28*β*** exhibits a shorter S−C3 bond (1.801 Å) relative to **9** and **20** and C3−O bond (1.441 Å) of intermediate length relative to acetoxythiopyranosides.[63b]

(59) For examples of X-ray crystal structures of α-aza derivatives, see: Koole, L. H.; Plavec, J.; Liu, H.; Vincent, B. R.; Dyson, M. R.; Coe, P. L.; Walker, R. T.; Hardy, G. W.; Rahim, S. G.; Chattopadhyaya, J. *J. Am. Chem. Soc.* **1992**, *114*, 9936–9943.

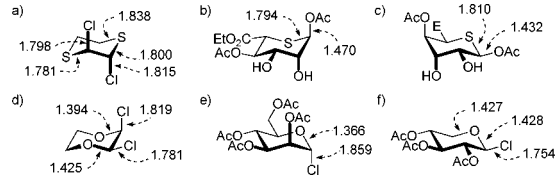


(60) Watts, J. K.; Sadalapure, K.; Choubdar, N.; Pinto, M. B.; Damha, M. J. *J. Org. Chem.* **2006**, *71*, 921–925.

(61) (a) *trans*-2,3-Dichlorotetrahydrothiophene: Delaney, P. A.; Johnstone, R. A. W. *Tetrahedron* **1985**, *41*, 3845–3851. (b) 2-Alkoxy-3-chlorotetrahydrothiophenes: Delaney, P. A.; Johnstone, R. A. W.; Leonard, P. A.; Regan, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 285–289. (c) *trans*-2,3-Dibromotetrahydrothiophene and 2-alkoxy-3-bromotetrahydrothiophenes: Wilson, G. E., Jr.; Albert, R. *J. Org. Chem.* **1973**, *38*, 2156–2159.

(62) The anomeric effect is generally thought to be strongest with electron-withdrawing substituents: halogen > OR > SR > OH > NR_2.[57c]

(63) The X-ray structures of the following derivatives were considered useful for comparison. Arrows indicate bond lengths (Å). (a) Kalff, H. T.; Romers, C. *Acta Crystallogr.* **1965**, *18*, 164–168. (b) Adam, D.; Freer, A. A.; Isaacs, N. W.; Kirby, G. W.; Littlejohn, A.; Rahman, M. S *J. Chem. Soc., Perkin Trans. 1* **1992**, 1261–1264. (c) Altona, C.; Romers, C. *Acta Crystallogr.* **1963**, *16*, 1225–1232. (d) Paulson, H.; Luger, P.; Heiker, F. R. In *Anomeric Effect: Origin and Consequences*; Szarek, W. A., Horton, D., Eds.; ACS Symposium Series 87; American Chemical Society: Washington, DC, 1979; Chapter 5 and references therein.



Interestingly, in contrast to **21α** and **28*β***, the X-ray crystal structure of the 3α-O*t*-Bu derivative **25α** shows a long S−C3 bond (1.844 Å) and a short C3−O bond (1.395 Å). This is consistent with the general consensus that anomeric effects are stronger with oxygen than sulfur.[57,58,64]

Computational Results. Ab initio (RHF/6-31G(d)) molecular orbital (MO) calculations[65] were carried out with several of the cyclobutanone derivatives that had been prepared synthetically (Table 4). As expected, the conformational preferences observed by NMR (solution phase) and by X-ray (solid state) were also found in the gas phase, and the preferred conformations favor C3 substitutents axial orientations.

In order to gain additional insight into the origin of the conformational preferences and putative stereoelectronic stabilizations of axial arrangements, additional calculations were performed with a series of simplified cyclobutanone derivatives that lack the C4-carboxylate moiety.

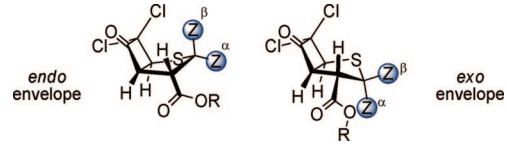
Interestingly, these calculations show that the C4-carboxylate has a minor effect on the conformations of unsubstituted (Z = H) cyclobutanones, as each of the cyclobutanones **9** and **18**−**20** (1.4−1.9 kcal/mol) and **33** and **34**[66] (2 kcal/mol) have a significant preference for the *endo* envelope, and suggest that the eclipsing interactions between substituents at C4 and C5 in the *exo* envelope are significant (Figure 8).[67]

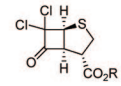
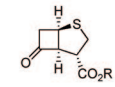
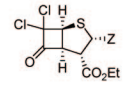
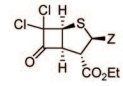
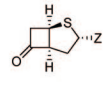
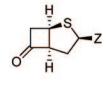
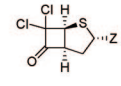
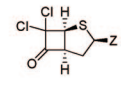
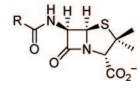
Computational evidence of the anomeric effect is noted in the comparison of cyclobutanones **33** and **34** to compounds with α substituents at C3. The small preference for the *exo* envelope (0.05 kcal/mol) shown by cyclobutanone **35α**, for example, indicates that the energy gained by stereoelectronic stabilization in the *exo* envelope is enough to overcome the natural *endo* preference (1.89 kcal/mol) of the fused bicycle. Thus, comparison of **33** with **35α**−**39α** suggests that anomeric effects could be worth up to 1.9, 3.3, 3.1, 1.5, and 1.1 kcal/mol for Z = α-Cl, α-OAc, α-OMe, α-O*t*-Bu, and α-SMe, respectively. Similar trends were found with the dichlorocyclobutanones **40α**, **41α**, and **42α**, which gave values of 1.9, 3.2, and 1.0 kcal/mol for Z = α-Cl, α-OMe, and α-SMe, respectively, when compared to **34**.

Calculations involving *β*-substituents at C3 also indicate that an anomeric effect is present, as the *β*-alkoxy derivatives **36*β***−**38*β*** show increased preferences for the *endo* envelope (2.8, 2.6, and 1.4 kcal/mol for Z = *β*-OAc, *β*-OMe, and *β*-O*t*-Bu) relative to **33** (Z = H). However, the *β*-Cl derivative **35*β***, which contains a sterically larger substituent, shows only a modest increase in *endo* preference (0.2 kcal/mol), and the *β*-SMe analogue **39*β*** shows a decrease in *endo* preference (1.0 kcal/mol). Since this pattern is magnified in the 7,7-dichloro series **40*β***−**42*β*** (−0.8, +2.4, and −1.9 kcal/mol for *β*-Cl, *β*-OMe, and *β*-SMe compared to **34**), it seems reasonable to conclude that large 3*β*-substituents experience a significant steric interaction with the 7*β*-H or 7*β*-Cl (Figure 8).[68]

Given the large magnitudes of the calculated conformational preferences (2−5 kcal/mol) for cyclobutanones **21**−**25**, **28**, and **32** and the relatively small preferences with derivatives **35α**−**39α**, and **40α**−**42α**, it is clear that the C4-carboxylate moiety significantly enhances the preference for the *exo* conformation with α-substituents. It is likely that a disfavored steric interaction between the 3α-Z function and the carboxylate

TABLE 4. Calculated Conformational Preferences for Cyclobutanone and *β*-Lactam Derivatives[a]



Cyclobutanone or β-Lactam [b]		Relative Energy (kcal) *endo*	*exo*
	**9**: R = H	0	+1.93
	18: R = Et	0	+1.92
	30: R = –	0	+2.28
	**19**: R = Et	0	+1.43
	20: R = H	0	+1.44
	31: R = –	0	+1.73
	**21α**: Z = Cl	+2.44	0
	22α: Z = OH	+3.84	0
	23α: Z = OMe	+3.75	0
	25α: Z = O*t*-Bu	+1.29	0
	28α: Z = OAc	+3.41	0
	32α: Z = SMe	+0.55	0
	**21β**: Z = Cl	0	+1.69
	22β: Z = OH	0	+5.18
	23β: Z = OMe	0	+4.85
	25β: Z = O*t*-Bu	0	+3.55
	28β: Z = OAc	0	+4.78
	32β: Z = SMe	0	+0.64
	**33**: X = H	0	+1.89
	34: X = Cl	0	+2.42
	**35α**: Z = Cl	+0.05	0
	36α: Z = OAc	+1.40	0
	37α: Z = OMe	+1.17	0
	38α: Z = O*t*-Bu	0	+0.35
	39α: Z = SMe	0	+0.75
	**35β**: Z = Cl	0	+2.08
	36β: Z = OAc	0	+4.64
	37β: Z = OMe	0	+4.46
	38β: Z = O*t*-Bu	0	+3.33
	39β: Z = SMe	0	+0.92
	**40α**: Z = Cl	0	+0.47
	41α: Z = OMe	+0.77	0
	42α: Z = SMe	0	+1.42
	**40β**: Z = Cl	0	+1.59
	41β: Z = OMe	0	+4.84
	42β: Z = SMe	0	+0.51
	**43:** R = Me	0	+2.05
	44: R = CH_2Ph	0	+2.18

[a] Structure optimizations (RHF/6-31G(d)) used Gaussian-03[65] and comparison of the relative electronic energy of each conformer was done following zero-point energy corrections. [b] Cyclobutanones **30**−**44** were used for calculations only and were not prepared in this study.

(64) (a) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G W *J. Am. Chem. Soc.* **1986**, *107*, 6393–6394. (b) Salzner, U.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1993**, *115*, 10231–10236. (c) Trapp, M. L.; Watts, J. K.; Weinberg, N.; Pinto, B. M. *Can. J. Chem.* **2006**, *84*, 692–701.

(65) Frisch, M. J. et al., *Gaussian-03, Revision B.04.*; Gaussian Inc.: Pittsburg, PA, 2003.

(66) The structure of **34** has been solved previously by a single-crystal X-ray study: Lange, G. M. Sc. Thesis, University of Waterloo, 1984.

(67) The *endo* envelope is also favored with 2-oxa and 2-carba analogues (**43**−**46**) of **33** and **34**. See Table S1 in Supporting Information.

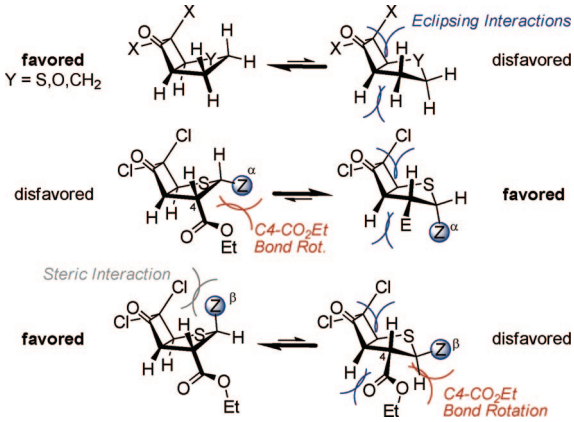


FIGURE 8. Favored conformations and relevant steric interactions.

in the *endo* envelope accounts for much of this energy since a significant rotation of the C4−CO_2Et bond[69] is observed in the optimized *endo* envelope conformations of **23α**, **25α**, **28α**, and **32α** and not in the *exo* envelope conformations.[70] Comparison of the conformational preferences of cyclobutanones with *β*-substituents, however, indicates that the carboxylate has a minor effect, as **21*β***, **23*β***, and **32*β*** have nearly identical preferences as the decarboxy analogues **40*β***−**42*β***.

In addition to the computational results described thus far, the conformational preferences of several 2-oxa and 2-carba (CH_2) analogues have been calculated for the purpose of comparison (Table S1, Supporting Information). It is worth noting that the calculated conformational preferences for the 2-thia series are generally larger in magnitude than the preferences of the 2-oxa counterparts, and that this is likely a consequence of increased steric interactions in the tetrahydrofuran system due to the shorter endocyclic carbon−oxygen bond lengths.

Conformations of Penicillins. The importance of the penicillins to antibiotic therapy has led to numerous studies of their three-dimensional structures by experimental and theoretical methods, and particular attention has been paid to the conformational properties of the thiazolidine ring. X-ray crystal structures, which have been obtained for a variety of penicillins, show that the bicycle can adopt an *endo* envelope conformation **I** or an *exo* envelope conformation **J** (Figure 9).[71] The *endo* and *exo* envelopes are also referred to as the C3-puckered and *S*-puckered conformations, based on the atom that is most out of the plane of the ring, or the axial and equatorial conformations, respectively, based on the orientation of the 3α-carboxylate.

Attempts have been made to correlate the solid-state conformational preferences with biological activity,[72,73] but NMR

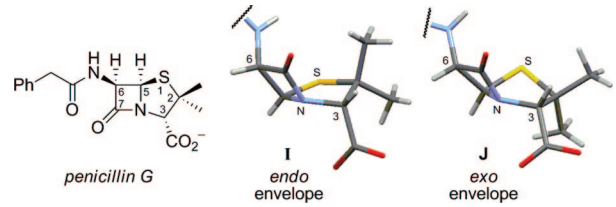


FIGURE 9. Two conformations of penicillin G.[71] Figures of the *endo* envelope (C3-puckered, axial) conformation **I** and the *exo* envelope (*S*-puckered, equatorial) conformation **J** were adapted from X-ray crystal structures of the potassium salt (CCDC: BPENK01) and the procaine salt (CCDC: PRPENG), respectively.

studies by Dobson et al. demonstrate that these differences in conformational preference are not present in solution. The use of lanthanide ions as probes[74] and ^{13}C cross polarization magic angle spinning (CP-MAS) NMR experiments[75] indicate that several penicillins (with different solid-state preferences) all favor the *exo* envelope conformation **J** in aqueous solution with ratios of *endo*:*exo* conformers ranging from 45:55 to 21:79, respectively.[76]

While penicillin G has been found to favor the *endo* envelope conformation **I** in the gas phase by several computational studies[77] including our own (2.2 kcal/mol, Table 4), molecular dynamics (MD) studies by Díaz et al.[77a] show that solvent has a significant energetic effect (∼1.5 kcal/mol) in stabilizing the *exo* envelope conformation **J**, and the MD simulation that predicts an *endo*:*exo* ratio of 70:30 in aqueous solution is in reasonable agreement with Dobson's experimental results.

In the context of biological activity, it is thought that *β*-lactamases preferentially bind to the *exo* envelope conformer **J** of penicillins. Through detailed MD simulations of penicillin G complexed with the class A TEM-1 *β*-lactamase, Díaz et al. have shown that H-bonding interactions between the C3-carboxylate and Ser130, Ser235, and Arg244 are favored with the equatorial conformer **J** and that a steric clash between the 2*β*-methyl group and Ala237 is also avoided.[78] Additional molecular modeling studies involving mechanisms of penicillin acylation in TEM-1 (class A)[79] and P99 (class C)[80] *β*-lactamases have also involved the *exo* envelope conformation **J** of the penicillins, but analogous studies with the class B and class D enzymes have yet to be reported.

Of additional interest is the fact that a noncovalent complex between the R61 transpeptidase and a peptidoglycan-mimetic penicillin has been trapped crystallographically, and the X-ray

(68) It should be noted, however, that the distances measured between the 3*β*-Z atom and the 7*β*-X atom were longer than van der Waals contacts in each of the optimized structures. For van der Waals radii, see: Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451. Carbon 1.70 Å; oxygen 1.52 Å; sulfur 1.80 Å; chlorine 1.75 Å.

(69) The lowest energy conformations show a dihedral angle of close to 0° between the C4-C5 bond and the C=O bond of the ester.

(70) A plot of potential energy vs dihedral angle, generated by a torsional scan calculation, is provided in Supporting Information for cyclobutanone **18** in each of the *endo* and *exo* conformations (Figure S1).

(71) Dexter, D. D.; van der Veen, J. M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 185–190.

(72) (a) Cohen, N. C. *J. Med. Chem.* **1983**, *26*, 259–264. (b) Balsamo, A.; Domiano, P.; Macchia, B.; Nardelli, M. *Eur. J. Med. Chem.* **1980**, *15*, 559–562.

(73) The assumption that *β*-lactam solid-state conformations represent solution phase conformations has been questioned: Koch, A.; Kühne, R.; Franke, R. *Pharmazie* **1990**, *45*, 694–695.

(74) Dobson, C. M.; Ford, L. O.; Summers, S. E.; Williams, R. J. P. *J. Chem. Soc., Chem. Commun.* **1975**, *71*, 1145–1153.

(75) (a) Clayden, N. J.; Dobson, C. M.; Lian, L.-Y.; Twyman, J. M. *J. Chem. Soc., Perkin Trans 2* **1986**, 1933–1940. (b) Twyman, J. M.; Fattah, J.; Dobson, C. M. *J. Chem. Soc., Chem. Commun. 2* **1991**, 647–649.

(76) A spin-labeled penicillin was also found to adopt an *exo* envelope conformation in solution: Mustafi, D.; Makinen, M. W. *J. Am. Chem. Soc.* **1995**, *117*, 6739–6746.

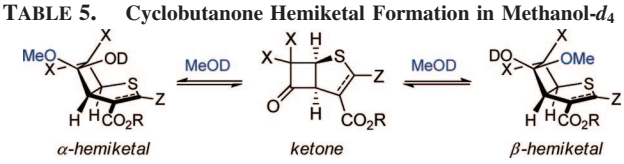
(77) (a) Díaz, N.; Suárez, D.; Sordo, T. L. *J. Comput. Chem.* **2003**, *24*, 1864–1873. (b) Peña-Gallego, A.; Cabaleiro-Lago, E. M.; Fernández-Ramos, A.; Hermida-Ramón, J. M.; Martínez-Núñez, E. *J. Mol. Struct. (Theochem)* **1999**, *491*, 177–185. (c) Frau, J.; Coll, M.; Donoso, J.; Muñoz, F. *J. Mol. Struct. (Theochem)* **1991**, *231*, 109–124. (d) Joshi, N. V.; Virudachalam, R.; Rao, V. S. R. *Curr. Sci.* **1978**, *47*, 933–936.

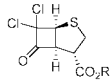
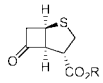
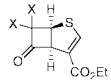
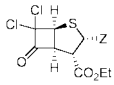
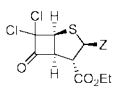
(78) Díaz, N.; Sordo, T. L.; Merz, K. M., Jr.; Suárez, D. *J. Am. Chem. Soc.* **2003**, *125*, 672–684.

(79) (a) Meroueh, S. O.; Fisher, J. F.; Schlegel, B.; Mobashery, S. *J. Am. Chem. Soc.* **2005**, *127*, 15397–15407. (b) Hermann, J. C.; Hensen, C.; Ridder, L.; Mulholland, A. J.; Höltje, H.-D. *J. Am. Chem. Soc.* **2005**, *127*, 4454–4465. (c) Oliva, M.; Dideberg, O.; Field, M. J. *Proteins* **2003**, *53*, 88–100.

(80) Fenollar-Ferrer, C.; Frau, J.; Donoso, J.; Muñoz, F. *Proteins* **2003**, *51*, 442–452.

TABLE 5. Cyclobutanone Hemiketal Formation in Methanol-d_4



Cyclobutanone		α : β hemiketal ratio[b]	% hemiketal
	**9**: R = H	2.7 : 1	88
	18: R = Et	2.7 : 1	91
	**19**: R = Et	1.8 : 1	19
	20: R = H	1.6 : 1	24
	**26**: X = Cl	1.8 : 1	96
	27: X = H	1.5 : 1	38
	**23α**: Z = OMe	1.2 : 1	98
	24α: Z = O*i*-Pr	1.1 : 1	98
	25α: Z = O*t*-Bu	1.1 : 1	98
	**23β**: Z = OMe	4.7 : 1	15
	24β: Z = O*i*-Pr	4.2 : 1	24
	25β: Z = O*t*-Bu	1.8 : 1	40
	28β: Z = OAc	1.5 : 1	30

[a] The extent of hemiketal formation was determined by ^{1}H NMR experiments in neat CD_3OD. [b] The ratio was determined when the system had reached equilibrium.

structure shows that the penicillin adopts the *exo* envelope conformation **J**.[81]

Cyclobutanone Hemiketal Formation. Given the extensive computational evidence (above), which suggests that penicillins bind to β-lactamase active sites in the *exo* envelope conformation, and the large magnitude of the conformational preferences calculated in the present study for the 3-alkoxy cyclobutanone derivatives (Table 4), we wondered whether the conformation of the tetrahydrothiophene ring would have a significant effect on the tendency of the cyclobutanones to undergo hydrate and hemiketal formation.

Evaluation of hemiketal formation with cyclobutanones involved simple NMR experiments in which the cyclobutanone of interest was dissolved in neat methanol-d_4 (Table 5). As mentioned above, the dichlorocyclobutanones **9** and **18** (X = Cl) underwent hemiketal formation to a much greater extent than the dechlorinated ketones **19** and **20** (X = H). As expected, this pattern was also evident in the unsaturated system as hemiketal formation occurred to a greater extent with **26** (X = Cl) than with **27** (X = H).

Exposure of the 3-alkoxy dichlorocyclobutanones **23**−**25** and ***28β*** to methanol-d_4 revealed that the extent of hemiketal formation was highly dependent upon the steric environment surrounding the carbonyl. Thus, hemiketal formation is highly favored in cyclobutanones that prefer the *exo* envelope, **23α**−**25α** (98%), whereas hemiketal formation is less significant

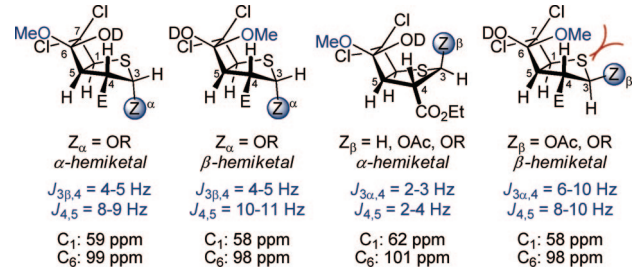


FIGURE 10. Conformations of cyclobutanone hemiketals as indicated by ^{1}H and ^{13}C NMR (R = Me, *i*-Pr, *t*-Bu).

with cyclobutanones **23*β***−**25*β*** and ***28β*** (15−40%), which adopt the *endo* envelope. It is reasonable that the unsaturated esters **26** and **27** show larger proportions of hemiketal than **18** and **19**, respectively, since the C3 methylene unit could impose additional steric congestion in the *endo* envelope.[82]

While it has been well established that nucleophilic attack on the carbonyl group is highly favored from the *exo* face of bicyclo[3.2.0]heptanones, the reversible nature of hemiketal formation gave rise to a mixture of the ketone and each of the α- and β-hemiketals that often required weeks to equilibrate. Tabulation of the equilibrium ratios of α-hemiketal/β-hemiketal revealed that the relative stability of the α- and β-hemiketals is highly sensitive to steric hindrance in the same way that the extent of hemiketal formation was found to be. Namely, the cyclobutanone derivatives with the greatest steric bulk on the *endo* face of the bicycle have the highest α/β-hemiketal ratios.

Interestingly, the coupling patterns in ^{1}H NMR and the chemical shifts observed in the ^{13}C NMR indicate that the β-hemiketals of 3β-alkoxy cyclobutanones **23*β***−**25*β*** and ***28β*** adopt the *exo* envelope conformation (Figure 10).[83]

Rate of Hemiketal Formation. In contrast to the fast hydrate formation observed with **9** (X = Cl) in D_2O and the classical study by Wiberg et al. involving carbonyl reactions,[43] hemiketal formation involving **9** and **18** was surprisingly slow given the high electrophilicity of the carbonyl carbon and required several hours to equilibrate.[84] The results reported by Wiberg et al., which show that hemiketal formation with ketones is fast, were replicated by our laboratory for cyclobutanone itself[85] and were also reflected in the relatively fast hemiketal formation demonstrated by the dechlorinated cyclobutanones **19** and **20**.

Although the extent of hemiketal formation is greater for the 7,7-dichlorinated systems as compared with the nonchlorinated compounds, our qualitative observations of relative rates of hemiketal formation suggest that the process is somewhat impeded by the halogen substituents.[86]

Hemiketal formation must involve either protonation of the carbonyl oxygen or at least substantial H-bonding to the oxygen from the solvent to activate the carbonyl for nucleophilic attack at carbon. The chlorine atoms at C7 likely diminish electron density on the carbonyl oxygen atom, making it less basic and

(81) The noncovalent complex of the R61 transpeptidase with a so-called perfect penicillin substrate was achieved by cross-linking the enzyme such that Lys65 and Tyr159 are restrained (PDB code 1PW1). Silvaggi, N. R.; Josephine, H. R.; Kuzin, A. P.; Nagarajan, R.; Pratt, R. F.; Kelly, J. A. *J. Mol. Biol.* **2005**, *345*, 521–533.

(82) Steric hindrance of hydration has been speculated previously for ketones with nearby *tert*-leucine sidechains (ref 36 and references therein).

(83) For tables of selected ^{1}H and ^{13}C NMR data for cyclobutanones and cyclobutanone hemiketals, see Tables S5−S7 (Supporting Information).

(84) Reaction rates were not determined quantitatively, but hemiketal formation was followed by NMR and plots of % hemiketal vs time have been supplied for each ketone in Supporting Information (Table S8).

(85) Our laboratory also found that hemiketal formation with cyclobutanone (25 mg) in CD_3OD (1 g) is fast, as equilibrium was achieved in 15 min at ambient temperature and 4.5% hemiketal was formed (by ^{1}H NMR at 500 MHz).

(86) The approximate trend in relative rates of hemiketal formation is **23α**−**25α** > **27** ≈ **26** ≈ **19** > **18** > ***25β*** > ***24β*** > ***23β***.

less prone to protonation by an acid catalyst or to act as an H-bond acceptor. Furthermore, the chlorines likely offer a degree of steric hindrance to the solvation that might be required for lowering the activation energy for the addition step in hemiketal formation.

Conclusions

The analysis presented above reveals a strong influence of C3 substitution on the conformational preferences of the 2-thiabicyclo[3.2.0]heptan-6-one ring system and also on rate and extent of hemiketal formation. The stereochemistry at C3 plays a crucial role in determining the conformational preferences of the five-membered ring, and steric influences, including steric hindrance of solvation, have been implicated in controlling the rate and extent of hemiketal formation. In addition, within the observations outlined above are, to our knowledge, some of the clearest demonstrations of anomeric effects in tetrahydrothiophene systems.

The design of cyclobutanones as potential β-lactamase inhibitors (or for interaction with other penicillin-binding proteins) might well benefit from an ability to predict the extent to which the structure of the cyclobutanone best suits the nature of the interactions of the biological target with the normal β-lactam substrates. The detailed computational studies[78−80] that involve the acylation of class A and C serine β-lactamases indicate that the reaction pathway involves *exo* attack of the active-site serine on the β-lactam carbonyl with the thiazolidine ring of the penicillin in the *exo* envelope conformation. The analysis of the conformational preferences of the cyclobutanones examined in the present study would suggest that a 2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylate that either lacks a substituent at C3 or one that incorporates a 3β substituent would be a poor choice for the task of mimicking the tetrahedral intermediate-forming step of the catalytic process since both of these systems favor the *endo* envelope conformation. On the other hand, such systems incorporating a 3α substituent exhibit a substantial preference for an *exo* envelope conformation. Furthermore, these systems exhibit a tendency to form hemiketals relatively rapidly and completely, which are properties desirable for a potential β-lactamase inhibitor functioning by the mechanism suggested by the theoretical studies indicated above.

The details of the interactions of other penicillin-sensitive enzymes with their targets is not entirely clear, and it is conceivable that the preferences of these other targets for the conformations of the substrate may differ so that an understanding of the properties of potential cyclobutanone mimics might prove valuable in fine-tuning the properties of such compounds for affinity for specific targets.

Experiments designed at exploiting these observations in the context of design of β-lactamase inhibitors are under way in this laboratory,[87,88] but the potential for broader application of these concepts in the specific design of related compounds targeting other penicillin targets elsewhere is certainly encouraged.

Experimental Section

7,7-Dichloro-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylic Acid (9). Ethyl ester **18** (1.323 g, 4.916 mmol) was dissolved in dioxane (10 mL) and stirred with 6 M HCl (20 mL) at 80 °C for 6 h. The reaction mixture was cooled to room temperature, extracted with CH_2Cl_2 (3 × 20 mL), and dried with Na_2SO_4 before the solvent was removed in vacuo. The crude beige-colored solid was recrystallized from PhMe to give dichlorocyclobutanone **9** (936.1 mg, 3.883 mmol, 79%) as light yellow needles. Mp 160−161 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 3.06 (dd, J_{gem} = 12.4 Hz, $J_{3\beta,4}$ = 5.9 Hz, 1H, $H_{3\beta}$), 3.50 (d, J_{gem} = 12.4 Hz, 1H, $H_{3\alpha}$), 3.81 (d, $J_{4,3\beta}$ = 5.9 Hz, 1H, H_4), 4.69 (d, $J_{1,5}$ = 8.5 Hz, 1H, H_1), 5.14 (d, $J_{5,1}$ = 8.5 Hz, 1H, H_5). ^{13}C NMR (75.5 MHz, acetone-d_6): δ 36.3, 50.7, 59.5, 68.6, 90.2, 171.3, 196.0. IR (film, cm^{-1}): br 3200−2600, 2951, 1810, 1700, 1453, 1417, 1262, 1190. LRMS (EI) *m/z* (relative intensity): 244 ($M[(^{37}Cl_2)]^+$, 5), 242 ($[M(^{37}Cl^{35}Cl)]^+$, 27), 240 ($[M(^{35}Cl_2)]^+$, 38), 222 (10), 194 (20), 180 (60), 141 (40), 130 (40), 85 (100). HRMS (EI) *m/z*: 239.9415 calcd for $C_7H_6{}^{35}Cl_2O_3S$; 239.9421 obsd.

2-Thiabicyclo[3.2.0]heptan-6-one-4-carboxylic Acid (20). Zinc dust (293.4 mg, 4.486 mmol) was added to a stirring solution of dichlorocyclobutanone **9** (212.1 mg, 0.8798 mmol) in glacial acetic acid (25 mL) at room temperature before it was heated to 80 °C. An additional portion of zinc dust was added after 1.5 h (293.0 mg, 4.481 mmol), and the suspension was stirred for an additional 16 h before it was cooled to room temperature. The solution was diluted with EtOAc (100 mL) and filtered through glass wool to remove residual solid before concentration under reduced pressure. The resulting oil was redissolved in EtOAc (50 mL) and washed with 10% HCl (2 × 50 mL). The organic phase was then dried over Na_2SO_4 and the solvent removed under reduced pressure. Trituration with CH_2Cl_2/hexane provided **20** as a white solid (134.0 mg, 0.7782 mmol, 88%). Mp 98−100 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 2.85 (ddd, J_{gem} = 18.4 Hz, $J_{7\beta,1}$ = 3.2 Hz, $J_{7\beta,5}$ = 3.2 Hz, 1H, $H_{7\beta}$), 3.22 (dd, J_{gem} = 12.1 Hz, $J_{3\beta,4}$ = 5.9 Hz, 1H, $H_{3\beta}$), 3.44 (d, J_{gem} = 12.1 Hz, 1H, $H_{3\alpha}$), 3.56 (d, $J_{4,3\beta}$ = 5.9 Hz, 1H, H_4), 3.70 (ddd, J_{gem} = 18.3 Hz, $J_{7\alpha,1}$ = 8.2 Hz, $J_{7\alpha,5}$ = 3.5 Hz, 1H, $H_{7\alpha}$) 4.17 (ddd, $J_{1,5}$ = 8 Hz, $J_{1,7\alpha}$ = 8.2 Hz, $J_{1,7\beta}$ = 3.5 Hz, 1H, H_1), 4.64 (m, 1H, H_5). ^{13}C NMR (75.5 MHz, acetone-d_6): δ 35.6, 37.5, 50.3, 56.6, 72.3, 172.4, 208.4. IR (film, cm^{-1}): br 3200−2600, 2933, 1780, 1705, 1383, 1252. LRMS (EI) *m/z* (relative intensity): 174 ($[M + 2]^+$, 2.7), 173 ($[M + 1]^+$, 4.4), 172 (M^+, 49), 130 (65), 97 (10), 85 (100). HRMS (EI) *m/z*: 172.0194 calcd for $C_7H_8O_3S$; 172.0191 obsd.

Ethyl 3α,7,7-Trichloro-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate (21α). To a stirring solution of dichlorocyclobutanone **18** (1.005 g, 3.735 mmol) in dry CH_2Cl_2 (45 mL) at 0 °C was added

(87) Hydrolysis of the ethyl ester functionality (in **23**, for example) cannot be achieved cleanly in basic (NaOH) or acidic (HCl) conditions due to the sensitivity of the dichlorocyclobutanone ring and the *S,O*-acetal functionalities, respectively. Our group is currently pursuing the synthesis of the free acids via alternative esters that can be cleaved under mild conditions so that biochemical assays may be conducted.

(88) It should be noted that the development of cyclobutanone analogues of β-lactam antibiotics into therapeutically useful β-lactamase inhibitors will require attention to numerous issues beyond those associated with the tendency of such compounds to form hydrates or hemiketals in the active sites of metallo- or serine β-lactamases, respectively. For example, drug candidates that rely on an electrophilic functionality may be prone to inactivation by natural electrophile scavengers such as glutathione and might exhibit toxic side effects arising from nonspecific covalent modification of biomolecules in the host.[89,90] Earlier in vitro studies of inhibition of serine proteases by electrophilic aldehydes and ketones[91] have revealed, however, that k_{off} for such reversible inhibitors can be substantially decreased and selectivity increased with appropriate structural modifications of the inhibitors which increase their affinity for the enzyme through specific favorable hydrogen bonds and van der Waals contacts with active-site residues. A reviewer is thanked for constructive comments in this regard.

(89) For examples of drug leads which incorporate ketone functionalities, see ref 37 and (a) Romero, F. A.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 14004–14005. (b) Hardouin, C.; Kelso, M. J.; Romero, F. A.; Rayl, T. J.; Leung, D.; Hwang, I.; Cravatt, B. F.; Boger, D. L. *J. Med. Chem.* **2007**, *50*, 3359–3368. (c) Wegener, D.; Hildmann, C.; Riester, D.; Schober, A.; Myer-Almes, F.-J.; Deubzer, H. E.; Oehme, I.; Witt, O.; Lang, S.; Jaensch, M.; Makarov, V.; Lange, C.; Busse, B.; Schwienhorst, A. *Biochem. J.* **2008**, *413*, 143–150.

(90) For an overview of potential difficulties with drug candidates that incorporate ketone functionalities, see: Rishton, G. M. *Drug Discov. Today* **2003**, *8*, 86–96.

(91) For examples of enhancement of inhibitory potency by structural modifications of electrophilic ketone-based protease inhibitors, see refs 35b and 40h and Brady, K.; Abeles, R. H. *Biochemistry* **1990**, *29*, 7608–7617.

a solution of SO_2Cl_2 (1 M in CH_2Cl_2, 4.50 mL, 4.50 mmol). The solution was stirred at room temperature for 4 h before it was concentrated under reduced pressure to give **21α** as a white crystalline solid (1.132 g, 3.729 mmol, 99.8%). Mp 84−87 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.97 (dd, $J_{4,3}$ = 4.8 Hz, $J_{4,5}$ = 5.8 Hz, 1H, H_4), 4.23 (B of ABX_3, J_{AB} = 10.8 Hz, J_{BX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.26 (A of ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.94 (d, $J_{1,5}$ = 8.3 Hz, 1H, H_1), 5.20 (dd, $J_{5,1}$ = 8.3 Hz, $J_{5,4}$ = 5.8 Hz, 1H, H_5) 5.87 (d, $J_{3\beta,4}$ = 4.8 Hz, 1H, $H_{3\beta}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0, 59.8, 60.0, 62.5, 65.5, 74.1, 85.0, 166.2, 192.0. IR (film, cm^{-1}): 2985, 1815, 1740, 1372, 1266, 1236, 1212. LRMS (EI) *m/z* (relative intensity): 306 ($M[(^{37}Cl_2{}^{35}Cl)]^+$, 1), 304 ($[M(^{37}Cl^{35}Cl_2)]^+$, 2), 302 ($[M(^{35}Cl_3)]^+$, 2), 267 (10), 259 (15), 207 (100), 169 (50), 131 (55), 99 (90). HRMS (EI) *m/z*: 301.9338 calcd for $C_9H_9{}^{35}Cl_3O_4S$; 301.9336 obsd.

Ethyl 7,7-Dichloro-3*β*-hydroxy-2-thiabicyclo[3.2.0]heptan-6-one-4-carboxylate (22*β*). A solution of the trichlorocyclobutanone **21α** (57.5 mg, 0.189 mmol) in MeCN (2 mL) was added slowly dropwise to a stirring solution of AgOTf (60.1 mg, 0.234 mmol) in MeCN (5 mL) and H_2O (2 mL). The mixture was stirred for 4 h at room temperature before it was concentrated under reduced pressure, diluted with CH_2Cl_2 (25 mL) and filtered through Celite. The resulting yellow oil was subjected to flash chromatography (10% EtOAc/hexane), which provided a colorless oil (48.6 mg, 0.170 mmol, 90%) that was determined to be an 88:6:6 mixture of the thiolactol **22*β***, epimer **22α**, and an oxa-thia-tricyclo-octane **22c**, respectively.

Thiolactol 22*β*. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 2.7−2.9 (brs, 1H, OH), 3.83 (s, 1H, H_4), 4.18 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.67 (d, $J_{1,5}$ = 8.5 Hz, 1H, H_1) 5.05 (d, $J_{5,1}$ = 8.5 Hz, 1H, H_5), 5.98 (s, 1H, $H_{3\alpha}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 59.3, 59.8, 62.3, 65.0, 86.0, 90.4, 167.9, 193.1. IR (film, cm^{-1}): br 3600−3300, 2984, 1815, 1732, 1246, 1213, 1024. LRMS (EI) *m/z* (relative intensity): 288 ($M[(^{37}Cl_2)]^+$, 0.4), 286 ($[M(^{37}Cl^{35}Cl)]^+$, 5), 284 ($[M(^{35}Cl_2)]^+$, 8.0), 238 (15), 203 (50), 195 (75), 151 (85), 115 (100). HRMS (EI) *m/z*: 283.9677 calcd for $C_9H_{10}{}^{35}Cl_2O_4S$; 283.9681 obsd.

Epimer 22α. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (3H, $CO_2CH_2CH_3$), 2.7−2.9 (1H, OH), 3.70 (dd, $J_{4,3\beta}$ = 4.6 Hz, $J_{4,5}$ = 4.8 Hz, 1H, H_4), 4.18 (2H, $CO_2CH_2CH_3$), 4.79 (d, $J_{1,5}$ = 8.4 Hz, 1H, H_1), 5.08 (dd, $J_{5,1}$ = 8.4 Hz, $J_{5,4}$ = 4.8 Hz, 1H, H_5), 5.84 (d, $J_{3\beta,4}$ = 4.6 Hz, 1H, $H_{3\beta}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 57.0, 58.7, 61.6, 65.7, 86.2, 87.0, 166.8, 192.3.

Oxa-thia-tricyclo-octane 22c. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (3H, $CO_2CH_2CH_3$), 2.7−2.9 (1H, OH), 3.7 (m, 1H, H_4), 3.97 (m, 1H, H_5), 4.18 (m, 2H, $CO_2CH_2CH_3$), 4.26 (m, 1H, H_1), 5.87 (m, 1H, $H_{3\alpha}$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 50.1, 55.2, 56.4, 62.3, 86.8, 90.6, 105.7, 168.4.

Alternatively, **22*β*** could be obtained by hydrolysis of **21α** without AgOTf. H_2O (15 mL) was added to a solution of the 3α-Cl cyclobutanone **21α** (769.2 mg, 2.534 mmol) in MeCN (15 mL). After stirring at room temperature for 48 h, the solution was concentrated in vacuo to a yellow oil. Flash chromatography (10% EtOAc/hexane) afforded a colorless oil (543.2 mg, 1.905 mmol, 75%) with spectral properties identical to those of the material prepared in ROH/MeCN: an 88:6:6 mixture of **22*β***, **22α**, and **22c**.

Representative Procedure for Solvolysis of 21α in ROH/MeCN (Table 2). Ethyl 7,7-Dichloro-3α-methoxy-2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylate (23α). The 3α-chlorocyclobutanone **21α** (102.2 mg, 0.337 mmol) was dissolved in MeCN (5 mL) and stirred with MeOH (5 mL) at room temperature for 48 h. The solution was concentrated under reduced pressure to give a colorless oil that partially crystallized in vacuo. ^{1}H NMR of the crude mixture showed a product distribution of 75:24:1 for α-OMe(**23α**):*β*-OMe(**23*β***):**26**, respectively. Flash chromatography (5% EtOAc/hexane) provided **23α** (23.4 mg, 0.0782 mmol, 23%, 98% pure) and a 68:32 mixture of **23α** and **23*β*** (50.3 mg, 0.168 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.32 (s, 3H, OCH_3), 3.75 (app. t, $J_{4,3\beta}$ = 4.5 Hz, $J_{4,5}$ = 5.5 Hz, 1H, H_4), 4.17 (B of ABX_3, J_{AB} = 10.8 Hz, J_{BX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.26 (A of ABX_3, J_{AB} = 10.8 Hz, J_{AX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.66 (d, $J_{1,5}$ = 8.1 Hz, 1H, H_1), 5.17 (dd, $J_{5,4}$ = 5.5 Hz, $J_{5,1}$ = 8.1 Hz, 1H, H_5), 5.32 (d, $J_{3\beta,4}$ = 4.5 Hz, 1H, $H_{3\beta}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 56.7, 57.4, 58.7, 61.8, 66.4, 85.3, 97.4, 167.3, 193.4. IR (film, cm^{-1}): 2986, 2930, 2831, 1813, 1739, 1464, 1335, 1265, 1215, 1085, 1021. LRMS (EI) *m/z* (relative intensity): 302 ($M[(^{37}Cl_2)]^+$, 0.4), 300 ($[M(^{37}Cl^{35}Cl)]^+$, 1.5), 298 ($[M(^{35}Cl_2)]^+$, 2), 253 (20), 217 (10), 203 (20), 189 (20), 167 (60), 165 (100), 143 (50). HRMS (EI) *m/z*: 297.9833 calcd for $C_{10}H_{12}{}^{35}Cl_2O_4S$; 297.9827 obsd.

Representative Procedure for Substitutions Promoted by Silver Triflate (Table 3). Ethyl 7,7-Dichloro-3*β*-methoxy-2-thiabicyclo-[3.2.0]heptan-6-one-4-carboxylate (23*β*). The 3α-chlorocyclobutanone **21α** (104.1 mg, 0.343 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 10 min to a suspension of AgOTf (118.3 mg, 0.460 mmol), MeOH (75 μL, 1.841 mmol), and 3 Å MS (1 g) in CH_2Cl_2 (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 2 h and stirred for an additional 4 h at room temperature before dilution with CH_2Cl_2 and filtration through Celite. The filtrate was concentrated under reduced pressure, and ^{1}H NMR of the crude mixture showed a product distribution of 22:72:2:4 for α-OMe(**23α**):*β*-OMe(**23*β***):*β*-Cl(**21*β***):**26**, respectively. Flash chromatography (5% EtOAc/hexane) provided **23*β*** (29.7 mg, 0.099 mmol, 29%) and a 38:62 mixture of **23α**:**23*β*** (32.0 mg, 0.107 mmol, 31%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.34 (s, 3H, OCH_3), 3.82 (s, 1H, H_4), 4.19 (q, J = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.59 (d, $J_{1,5}$ = 8.6 Hz, 1H, H_1) 5.02 (d, $J_{5,1}$ = 8.6 Hz, 1H, H_5), 5.46 (s, 1H, $H_{3\alpha}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0, 56.3, 57.9, 59.4, 62.2, 64.9, 90.4, 95.2, 167.8, 192.7. IR (film, cm^{-1}): 2984, 2934, 2829, 1817, 1734, 1370, 1313, 1259, 1212, 1086. LRMS (EI) *m/z* (relative intensity): 302 ($M[(^{37}Cl_2)]^+$, 1), 300 ($[M(^{37}Cl^{35}Cl)]^+$, 5), 298 ($[M(^{35}Cl_2)]^+$, 8), 263 (30), 252 (20), 217 (40), 203 (100), 189 (90), 169 (55), 165 (55). HRMS (EI) *m/z*: 297.9833 calcd for $C_{10}H_{12}{}^{35}Cl_2O_4S$; 297.9836 obsd.

Ethyl 7,7-Dichloro-2-thiabicyclo[3.2.0]hept-3-ene-6-one-4-carboxylate (26). A solution of cyclobutanone **21α** (105.0 mg, was 0.346 mmol) in CH_2Cl_2 (2 mL) was slowly added to a stirring solution of AgOTf (104.1 mg, 0.405 mmol) in refluxing CH_2Cl_2 (20 mL) dropwise over 10 min. After 2 h at reflux, the solution was cooled to room temperature, diluted with CH_2Cl_2, filtered through Celite, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc/hexane) furnished the elimination product **26** as a colorless oil that crystallized under reduced pressure (74.4 mg, 0.279 mmol, 81%). Mp 75−76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 4.21 (B of ABX_3, J_{AB} = 10.7 Hz, J_{BX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.24 (A of ABX_3, J_{AB} = 10.7 Hz, J_{AX} = 7.1 Hz, 1H, one of $CO_2CH_2CH_3$), 4.89 (d, $J_{1,5}$ = 10.0 Hz, 1H, H_1) 5.43 (dd, $J_{5,1}$ = 10.0 Hz, $J_{5,3}$ = 1.7 Hz, 1H, H_5), 7.43 (d, $J_{3,5}$ = 1.7 Hz, 1H, H_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2, 59.6, 61.2, 71.3, 93.8, 122.2, 144.4, 161.1, 187.4. IR (film, cm^{-1}): 3075, 2984, 1812, 1705, 1576, 1370, 1327, 1238, 1078. LRMS (EI) *m/z* (relative intensity): 268 ($[M(^{37}Cl^{35}Cl)]^+$, 1.5), 266 ($[M(^{35}Cl_2)]^+$, 2.0), 238 (20), 203 (100), 175 (40). HRMS (EI) *m/z*: 265.9571 calcd for $C_9H_8{}^{35}Cl_2O_3S$; 265.9572 obsd.

Alternatively, the unsaturated ester **26** could be prepared from thiolactol **22*β***. $TsOH\cdot H_2O$ (10.9 mg, 0.057 mmol) was stirred in PhMe (40 mL) and heated at reflux under a Dean−Stark trap for 2 h.[92] The thiolactol **22*β*** (83.7 mg, 0.294 mmol) was then added as a solution in PhMe (2 mL) and stirred at reflux for an additional 18 h. The solution was concentrated under reduced pressure and purified by flash chromatography (10% EtOAc/hexane) to give a colorless oil that crystallized under vacuum (73.8 mg, 0.276 mmol, 94%).

(92) Incomplete conversion was observed when PhMe and TsOH were not predried.

Ethyl 2-Thiabicyclo[3.2.0]hept-3-ene-6-one-4-carboxylate (27). Dichlorocyclobutanone **26** (171.3 mg, 0.641 mmol) was dissolved in AcOH (15 mL), combined with zinc dust (216.0 mg, 3.303 mmol), and stirred at 80 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, and filtered through glass wool to remove residual zinc dust. The organic solution (75 mL) was washed with 10% HCl (2 × 75 mL) and brine (50 mL) before it was dried over Na_2SO_4 and concentrated. Flash chromatography (10% EtOAc/hexane) provided the dechlorinated cyclobutanone **27** as a colorless oil (106.5 mg, 0.537 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 3.34 (ddd, J_{gem} = 18.7 Hz, $J_{7\beta,1}$ = 5.7 Hz, $J_{7\beta,5}$ = 3.3 Hz, 1H, $H_{7\beta}$), 3.74 (ddd, J_{gem} = 18.7 Hz, $J_{7\alpha,1}$ = 8.3 Hz, $J_{7\alpha,5}$ = 5.1 Hz, 1H, $H_{7\alpha}$), 4.11−4.22 (m, 3H, H_1 and $CO_2CH_2CH_3$), 5.05−5.14 (m, 1H, H_5), 7.43 (s, 1H, H_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2, 37.0, 60.7 (2C), 76.0, 121.2, 143.2, 161.8, 200.0. IR (film, cm^{-1}): 3069, 2983, 1790, 1700, 1567, 1370, 1328, 1305, 1226. LRMS (EI) *m*/*z* (relative intensity): 200 ([M + 2]$^+$, 2), 199 ([M+1]$^+$, 5), 198 ([M]$^+$, 40), 170 (10), 156 (40), 141 (40), 128 (60), 111 (100), 97 (25). HRMS (EI) *m*/*z*: 198.0351 calcd for $C_9H_{10}O_3S$; 198.0349 obsd.

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Supporting Information Available: Experimental procedures and characterization data; ^{1}H and ^{13}C NMR spectra for **18**−**19**, new compounds, hydrate formation, and hemiketal formation; additional tables of calculated conformational and configurational preferences; total energies of modeled structures; Cartesian coordinates for optimized structure **D**; plots of the calculated energy of rotation around the C4−CO_2Et bond in **18**; tables of selected spectroscopic data for cyclobutanones and cyclobutanone hemiketals; tables and plots of percent hemiketal formation over time; crystallographic information files in CIF format and tables of crystallographic data for **9**, **20**, **21α**, **25α**, and **28*β***; complete reference 65. This material is available free of charge via the Internet at http://pubs.acs.org.

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